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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER				
TURK, NEIL N				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/524,615

Applicant(s)

MONTAGU ET AL.

Examiner

NEIL TURK

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,6,8,10,11,14-19,21,22,24,26,39,41 and 45 is/are pending in the application.
- 4a) Of the above claim(s) 39,41 and 45 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1,3,6,8,10,11,14-19,21,22,24 and 26 is/are rejected.
- 7) ☒ Claim(s) 10 is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 4/27/06, 2/16/05
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date ____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: ____

DETAILED ACTION

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1, 3, 6, 8, 10, 11, 14-19, 21, 22, 24, and 26 drawn to an array reader.

Group II, claim(s) 39 and 41, drawn to a diagnostic method.

Group III, claim(s) 45, drawn to a method of reading an array.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Groups II and III lack the corresponding special technical feature of group I in that neither recite an illumination system arranged at about 20 to 50 degrees to the plane of the substrate and the image collection and recording system of group I. Groups I and III lack the corresponding special technical feature of group II in that neither recite an array of different reagents respectively specific to bind members of biomarkers for diagnosing the selected disease, as recited in group II. Groups I and II lack the same corresponding special technical feature of group III in that neither recite intensity calibration features.

During a telephone conversation with John Williams on February 25th, a provisional election was made without traverse to prosecute the invention of group I, claims 1, 3, 6, 8, 10, 11, 14-19, 21, 22, 24, and 26. Affirmation of this election must be made by applicant in replying to this Office action. Claims 39,

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41, and 45 are withdrawn from further consideration by the examiner, 37

CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Objections

Claim 10 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Independent claim 1 calls for the same limitations as claim 10, as claim 1 recites that the image is of the same order of magnitude as the size of the array, i.e. not magnified.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 6, 8, 10, 11, 14-19, 21, 22, 24, and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Independent claim 1 recites that the image collection and recording system is enabled to record the image of fluorescence from the excited two-dimensional array, however such a recitation is unclear and undefined in that the claims do not recite that the photo-responsive markers are fluorescent markers. Thereby, this limitation to the image collection and recording system is not given patentable weight and such a limitation will be said to be met given prior art that recites all the positively recited structural elements in the claim, as the prior art would thereby be capable of such a function. Further, the relationship of the illumination path to that of the plane of the substrate is unclear as the particular plane of the substrate for such a relationship has not been definitely established in the claims in order to establish a defined relationship as intended.

Further, claim 1 is unclear as the image and recording system is recited to be, "constructed and arranged to apply an image . . . , e.g. within a range of magnification of up to about 25% or reduction down to 75%..." The recitation to the examples of such magnification and reduction are not properly recited. Use of the "e.g." clause within the claim does not properly and positively establish such limitations. This is further seen as a range within a range which thereby

lacks clarity. As such, the magnification in the range recited by the e.g. clause is not required to be disclosed in the prior art.

Claim 1 recites the limitation "the plane of the substrate". There is insufficient antecedent basis for this limitation in the claim.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear what the difference is between the intermediate numerical aperture of claim 1, and the effective aperture being recited in claim 3. Are these two different apertures? Is the value of NA between 0.3 and 0.60 merely the value for the intermediate numerical aperture of claim 1? Clarification is required. It is unclear if claim 3 recites a further element to the device of claim 1 to recite another numerical aperture, or if claim 3 is further defining the intermediate numerical aperture of claim 1. As currently recited, the range for NA will be taken to be the NA value of the aperture recited in claim 1.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear what is meant by "a diameter of the order of 10 mm or more". The combination of "of the order" and

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the open-ended range, by use of the term "or more", renders the range for the diameter unclear and undefined.

Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 18 recites a carrier for the array that comprises a substrate layer on a support body, then further recites that the substrate has a thickness less than about 5 micron[s]. This recitation is unclear as the claim is further establishing a substrate layer, but then recites the thickness of the substrate and not that of the substrate layer. The recitation is unclear as it does not parallel what is being further established and recited. Does Applicant intend to recite that the substrate layer (on the support body) has a thickness less than about 5 micron[s]?

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

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1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 8, 10, 17, 21, 24, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rava et al. (5,545,531), hereafter Rava, in view of Trulson et al. (5,578,832), hereafter Trulson.

Rava discloses a device for concurrently processing multiple biological chip assays. Rava discloses a biological chip plate reader 100 (illumination system for flooding the array between 20 to 50 degrees), biochip plate 120, and a computer 130 (column 4, figs. 1,2). Rava shows in figure 2 an excitation source 210 (a laser) for exciting the markers of the array (fluorescently labeled, CY3 or CY5 dyes, for example), and a CCD array and collection optics 240 (Examiner

asserts a CCD array and collection optics include a numerical aperture in a lens in order to provide such imaging) for detecting and generating signals, which are utilized to form a representative image (image-acquiring axis is substantially normal the substrate carrying the array), and further discloses a digital computer 270 for managing data collection (columns 5-8, fig. 2). Rava further discloses that the body of the biological chip and the substrate may be made transparent to the wavelengths of light being used and the biological chips may also be made to be light-absorbing, as it may be made from functionalized glass and surfaces of the substrate may be composed of different materials as the substrate, such as light-absorbing glass materials (columns 8&9, figs. 3&4). Rava further discloses that for fluorescein, sufficient signal-to-noise to read a chip image with a CCD detector can be obtained in about 30 seconds using a 3 mW/cm² and 488 nm excitation, and by increasing the laser power and using dyes such as CY3 or CY5, each well can be read in less than 5 seconds (lines 57-67, col. 6, figures 1-8).

Rava does not specifically disclose that the illumination system comprises at least one light-emitting diode. Rava also does not disclose that the illumination system includes a homogenizer.

Trulson discloses an apparatus for detecting a labeled marker on a sample located on a support, in which excitation radiation is utilized to excite an emission from the labeled material (abstract). Trulson discloses that the excitation radiation source may be, for example, light-emitting diodes (lines 11-21, col. 6, figures). Trulson further discloses that in some cases the light

produced by the array of LEDs may be nonhomogeneous, and light-shaping diffusers or fiber bundles are used to homogenize the excitation light.

It would have been obvious to modify Rava to include LEDs as excitations sources and a homogenizer such as taught by Trulson in order to provide a known, alternative form of an excitation source for use in exciting labeled probes or targets and a homogenizer for the purpose of avoiding producing non-homogenous excitation radiation from an array of LEDs so that the hybridization assay may be carried out more effectively and accurately.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rava in view of Trulson as applied to claims 1, 8, 10, 17, 21, 24, and 26 above and in further view of Mirzabekov et al. (5,851,772), hereafter Mirzabekov.

Rava/Trulson does not disclose that the image collection and recording system has an effective aperture between $NA = 0.3$ and $NA = 0.6$.

Mirzabekov discloses a microchip method for enrichment of specific DNA sequences (abstract). Mirzabekov discloses a multi-wavelength fluorescence microscope coupled with a CCD-camera for image analysis. Mirzabekov discloses an objective yielding a 3mm observation field enabled analysis of over 1,000 elements of the microchip at once and a numerical aperture of 0.4 allowed the illumination of the object field up to 7mm in diameter and projected 2.7x2.7mm of the microchip on the CCD matrix, and the same aperture allows for analyzing 5x5 microchip areas (lines 40-67, col. 10).

It would have been obvious to modify Rava/Trulson to include a numerical aperture of 0.4 such as taught by Mirzabekov in order to provide a numerical aperture known to be useful for imaging a wide area of elements on a microchip with fluorescently-labeled probes.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rava in view of Trulson as applied to claims 1, 8, 10, 17, 21, 24, and 26 above.

Rava/Trulson does not disclose an illumination to the array on the substrate of a power density greater than 30 mW/cm^2 .

It would have been obvious to modify Rava/Trulson to provide excitation illumination to the array on the substrate having a power density greater than 30 mW/cm^2 so as to allow for reading each well faster and thereby saving time in performing readings.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rava in view of Trulson as applied to claims 1, 8, 10, 17, 21, 24, and 26 above.

Rava/Trulson does not specifically disclose delivering to the solid state sensor array an image of the field of view reduced between about 30% and 50%.

Trulson discloses that resolution of the image may be manipulated by increasing or decreasing the magnification of the collection optics (col. 27).

It would have been obvious through routine experimentation to modify Rava/Trulson to deliver to the solid state sensor array an image of the field of

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view reduced between about 30% and 50% so as to provide optimal resolution of the image.

Claims 14 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rava in view of Trulson as applied to claims 1, 8, 10, 17, 21, 24, and 26 above and in further view of Mills, Jr. et al. (6,083,726), hereafter Mills, Jr..

Rava/Trulson does not specifically disclose that the carrier has a substrate layer, and further such a layer with a thickness less than about 5 microns.

Mills, Jr. discloses polynucleotide synthesis and articles for polynucleotide hybridization in which oligomers are attached to a substrate that includes a 0.5 micron thick layer of SiO₂ upon which to anchor the DNA oligomers (lines 39-67, col. 6).

It would have been obvious to modify Rava/Trulson to include a carrier with a substrate layer having a thickness less than about 5 microns such as taught by Mills, Jr. in order to provide a layer of suitable thickness on a substrate for anchoring probes for hybridization assays.

Claims 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rava in view of Trulson and in view of Mills, Jr. as applied to claims 1, 8, 10, 17, 14, 21, 24, and 26 above and in further view of Giaever (3,960,489).

Rava/Trulson/Mills, Jr does not specifically disclose a substantially opaque adherent layer between the substrate layer and transparent body, where the adherent opaque layer is a metal oxide.

Giaever discloses method for detecting biological particles (abstract).
Giaever discloses a metallized coating layer 10b (indium oxide, for example) that is between the substrate 10 (light transmissive, such as glass) and the first and second monomolecular layers 11a', 11b' (cols. 4&5, line 49, col. 10 – line 67, col. 11, figure 3b and figures 1-2b, & 4B). Giaever discloses that the metallized layer of indium oxide provides that the biomolecular layer is visible with good contrast to the unaided eye in order to visually assess the assay (abstract, cols. 4&5).

It would have been obvious to modify Rava/Trulson to include a metal oxide layer between the substrate layer and the transparent body such as taught by Giaever in order to provide a layer that allows for visible contrast with the biomolecular layer in order to visually assess resulting interactions on the chip.

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rava in view of Trulson as applied to claims 1, 8, 10, 17, 21, 24, and 26 above and in further view of Vo-Dinh et al. (6,197,503).

Rava/Trulson does not specifically disclose a substrate comprising a clear layer of nitrocellulose.

Vo-Dinh discloses attaching probe molecules or immobilized targets to a solid support such as nitrocellulose, in which hybridization is performed (lines 8-27, col. 2).

It would have been obvious to modify Rava/Trulson to include a substrate of a clear layer of nitrocellulose such as taught by Vo-Dinh in order to provide a support suitable for attaching targets or probes for hybridization.

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rava in view of Trulson as applied to claims 1, 8, 10, 17, 21, 24, and 26 above and in further view of Walton et al. (6,294,327), hereafter Walton.

Rava/Trulson does not specifically disclose two different light sources at different axes to the substrate.

Walton discloses an apparatus for detecting labeled samples (abstract; columns 3&4). Walton discloses that two light sources are used, one serving as a reflection mode light source and one serving as a diffuse scattering light source (illumination at 45 degrees in diffuse mode and at 20 degrees in reflection mode) (lines 55-67, col. 6, fig. 6). Walton also discloses that the light sources may be LEDs (lines 50-54, col. 5). Walton further discloses that a single linear CCD array, or multiple linear or area CCD arrays can be used to convert the scattered light image into an electrical signal which is converted to a voltage and then digitized by an A/D converter, in which the digital signal is stored in a computer as an image (lines 12-21, col. 7).

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It would have been obvious to modify Rava/Trulson to include two different light sources at different axes to the substrate such as taught by Trulson in order to provide an illumination system that would provide a more dynamic range of imaging of the array.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NEIL TURK whose telephone number is (571)272-8914. The examiner can normally be reached on M-F, 9-630.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on 571-272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NT

/Jill Warden/

Supervisory Patent Examiner, Art Unit 1797